



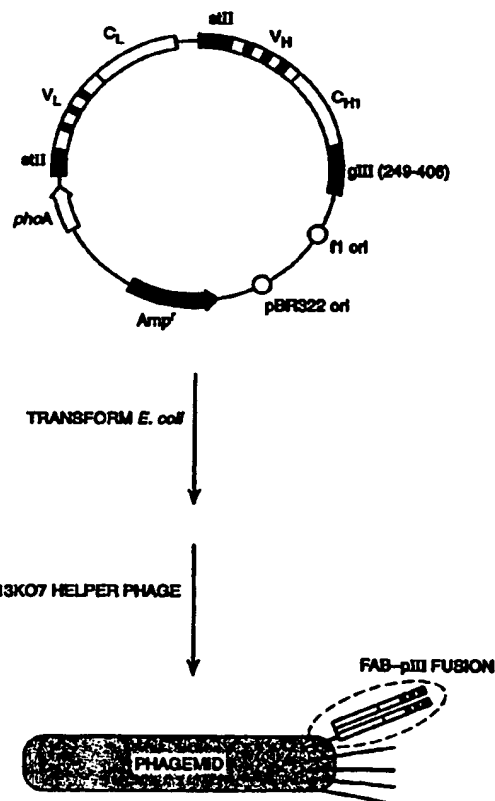
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 16/22, C12N 15/13, 15/63, 15/70, A61K 39/395	A3	(11) International Publication Number: WO 98/45331 (43) International Publication Date: 15 October 1998 (15.10.98)
<p>(21) International Application Number: PCT/US98/06604</p> <p>(22) International Filing Date: 3 April 1998 (03.04.98)</p> <p>(30) Priority Data: 08/833,504 7 April 1997 (07.04.97) US 08/908,469 6 August 1997 (06.08.97) US</p> <p>(71) Applicant (for all designated States except US): GENENTECH, INC. [US/US]; One DNA Way, South San Francisco, CA 94080 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BACA, Manuel [AU/US]; Apartment #H3, 888 Foster City Boulevard, Foster City, CA 94404 (US). WELLS, James, A. [US/US]; 1341 Columbus Avenue, Burlingame, CA 94010 (US). PRESTA, Leonard, G. [US/US]; Apartment 206, 1900 Gough Street, San Francisco, CA 94109 (US). LOWMAN, Henry, B. [US/US]; 400 San Juan Avenue, El Granada, CA 94018 (US). CHEN, Yvonne, Man-Yee [CA/US]; 1951 O'Farrell Street #321, San Mateo, CA 94403 (US).</p> <p>(74) Agents: DREGER, Walter, H. et al.; Flehr, Hobbach, Test, Albritton & Herbert LLP, Suite 400, 4 Embarcadero Center, San Francisco, CA 94111-4187 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p> <p>(88) Date of publication of the international search report: 3 December 1998 (03.12.98)</p>	

(54) Title: ANTI-VEGF ANTIBODIES

(57) Abstract

Humanized and variant anti-VEGF antibodies and various uses thereof are disclosed. The anti-VEGF antibodies have strong binding affinities for VEGF; inhibit VEGF-induced proliferation of endothelial cells *in vitro*, and inhibit tumor growth *in vivo*.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/06604

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K16/22 C12N15/13 C12N15/63 C12N15/70 A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 22653 A (GENENTECH INC) 23 December 1992	7, 10-13, 25-27
Y	the whole document and specially: see SEQ.ID.N. 17, 18 and 25 see page 5, line 24 - page 7, line 35 see page 9, line 22 - page 10, line 4; figure 5	1, 4, 14, 15, 22, 28-31, 34-38
Y	KIM ET AL.: "Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo" NATURE, vol. 362, 1993, page 841 XP002013864 London, GB cited in the application see abstract	1, 4, 14, 15, 22, 28-31, 34-38

-/-

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

18 September 1998

Date of mailing of the international search report

02/10/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Mateo Rosell, A.M.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/06604

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 268 744 A (CELLTECH LTD) 19 January 1994 see abstract see page 4, paragraph 3 - page 6, paragraph 1 ---	1,32-41
A	M.M. BENDIG: "Humanization of rodent monoclonal antibodies" METHODS: A COMPANION TO METHODS IN ENZYMOLGY, vol. 8, 1995, pages 83-93, XP000647344 New York, NY, US see the whole document ---	1,34-38
P,X	M. BACA ET AL., : "Antibody humanization using monovalent phage display" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 16, 18 April 1997, pages 10678-10684, XP002077471 see the whole document -----	1-42

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/06604

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5 AND 39-42
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 5 and 39-42
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/06604

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9222653 A	23-12-1992	AU 675916 B	27-02-1997
		AU 2250992 A	12-01-1993
		CA 2103059 A	15-12-1992
		EP 0590058 A	06-04-1994
		JP 6508267 T	22-09-1994
		WO 9404679 A	03-03-1994
GB 2268744 A	19-01-1994	AT 129017 T	15-10-1995
		AT 124459 T	15-07-1995
		AT 159299 T	15-11-1997
		AU 664801 B	30-11-1995
		AU 6461294 A	22-12-1994
		AU 646009 B	03-02-1994
		AU 6974091 A	24-07-1991
		AU 649645 B	02-06-1994
		AU 7033091 A	24-07-1991
		AU 631481 B	26-11-1992
		AU 7048691 A	24-07-1991
		BG 60462 B	28-04-1995
		CA 2037607 A	07-09-1992
		CA 2046904 A	22-06-1991
		CA 2050479 A,C	22-06-1991
		DE 69020544 D	03-08-1995
		DE 69020544 T	18-01-1996
		DE 69022982 D	16-11-1995
		DE 69022982 T	28-03-1996
		DE 69031591 D	20-11-1997
		DE 69031591 T	12-03-1998
		DK 460167 T	20-11-1995
		DK 460171 T	28-08-1995
		DK 460178 T	22-12-1997
		EP 0460167 A	11-12-1991
		EP 0460171 A	11-12-1991
		EP 0460178 A	11-12-1991
		EP 0620276 A	19-10-1994
		EP 0626390 A	30-11-1994
		ES 2079638 T	16-01-1996
		ES 2074701 T	16-09-1995
		ES 2112270 T	01-04-1998
		WO 9109966 A	11-07-1991

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/US 98/06604

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2268744 A		WO 9109967 A	11-07-1991
		WO 9109968 A	11-07-1991
		GB 2246781 A,B	12-02-1992
		GB 2246570 A,B	05-02-1992
		GB 2268745 A,B	19-01-1994
		GR 3017734 T	31-01-1996
		GR 3025781 T	31-03-1998
		JP 4505398 T	24-09-1992
		JP 4506458 T	12-11-1992
		JP 5500312 T	28-01-1993
